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EXAMINER
CHAKRABARTI, ARUN K

ART UNIT	PAPER NUMBER
1634	11

DATE MAILED: 07/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09763292	D. Hauzenberger
Examiner	**Group Art Unit**
A. Chakrabarti	1634

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE _____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 5-28-02.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1-18 is/are pending in the application.

Of the above claim(s) 4-18 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-3 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) / are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☒ Other Detailed Action

Office Action Summary

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group I, corresponding to claims 1-3, in Paper No. 10 is acknowledged. The traversal is on the ground(s) that "unity of invention" exists in the instant case because the methods of detecting mutation in a gene, the primers and kits are directed to isoforms of cytochrome P450 . This is not found persuasive because it has been made clear in the restriction requirement (Paper NO: 8) that primers for detecting mutations in cytochrome P450 isoforms are explicitly taught by Goldstein et al. (PCT International Publication Number WO 95/30766). Therefore, it is clear that all claims lack special technical feature and naturally no "unity of invention" exists. Moreover, the applicant argues that there is no burden in examining the claims of Groups I, II and II together. This is not found persuasive because as the restriction makes clear, additional search of Group II and III would require review not only of the 13,438 patents for Group I, but also the 1117 patents for Groups II and III. Review of these additional searches is prima facie evidence of burden which is not rebutted.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 1, the phrase "such as" on line 11 renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claims 1-3 are vague and indefinite over the recitation of the phrase, "known methods" in claim 1, line 6. The term "known methods" in claim 1 is a relative term which renders the claims indefinite. The term "known methods" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 1 is also rejected as indefinite because the instantly claimed method lacks a final process step that clearly relates back to the preamble. For the method of claim 1, the preamble of the instantly claimed methods are drawn to a method for determining the ability of cells in a sample to metabolize a certain drug while the final process step is that of detecting the incorporation of the nucleotide triphosphates whereby it is determined whether the sample contains the point mutation of the cytochrome P450 isoforms and it is thus unclear as to whether the instantly claimed method is drawn to a method for determining the ability of cells in a sample to metabolize a certain drug or rather detecting the incorporation of the nucleotide triphosphates

whereby it is determined whether the sample contains the point mutation of the cytochrome P450 isoforms. Method claim requires a last step or phrase in the last step that states the accomplishments of the goals for the method which were stated in the method's preamble. Claim 1 lacks such a last step and are confusing because the additional method step is not sufficiently set forth. While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashions. See Ex parte Erlich, 3 USPQ2d1011, p.1011 (Bd. Pat. Applicant. Int. 1986). It is suggested that an amended claim more clearly describing the intended steps be submitted.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement for determining the ability of any cells from any living organism or any cell culture to metabolize any drug. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The Court in re Wands, 8 USPQ2d 1400 (CA FC 1988) stated with regard to enablement that

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Here, the claim is broadly drawn to identifying the ability of any cells from any living organism or any cell culture to metabolize any drug. However, the specification does not provide guidance commensurate in scope with this claim, teaching only one human gene. The specification provides minimal guidance regarding methods for the identification of alternate drug metabolizing enzymes. There is no working example of any cells on which the claimed method was tested. It is highly unpredictable whether or what other cells would be detected in the context of a vast database of drugs. Further, identification of additional drug metabolizing capacity regiment will be by the trial and error method. This trial and error requirement is borne out because the effects of drugs on metabolites or small molecules of different cells of the physiological system cannot be readily deduced, even where the metabolic pathways are known. Further, each drug has unpredictable effects on metabolic function of different tissues and/or cells, and no general method for a priori selection of disease detection is presented. For example, Parkinson et al. (U.S. Patent 5,478,723) (December 26, 1995) teaches, "Consequently, the activity of the human P450 enzymes expressed in transfected beta-lymphoblastoid cells is usually

considerably less than that observed with human liver microsomes. Differences in the lipid environment, differences in enzyme insertion into the endoplasmic reticulum and differences in pool translational modifications of the enzymes are additional reasons why the activity of a human P450 enzyme expressed in beta-lymphoblastoid cells may differ from its activity in liver microsomes. For these and other reasons, negative results obtained with a cDNA expressed human P450 enzyme are difficult to interpret (Column 8, lines 43-53)". It would require a large amount of experimentation, potentially including the testing of thousands of cells for thousands of drugs, in order to identify additional metabolic pathways and other cellular associated factors with the claimed functionality. Given the Wand's factors opposing the full scope of enablement including the limited teaching in the specification, the absence of any working example, the teaching of unpredictability in the prior art, the unpredictability of the art, the breadth of the claim, and the large amount of experimentation needed, with only the skill level in the art being neutral towards enablement, it is concluded that undue experimentation is necessary to make and use the invention as broadly claimed.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-3 are rejected under 35 U.S.C. 103(a) over Soderlund et al. (PCT International Publication Number WO 91/13075) (September 5, 1991) in view of Goldstein et al. (PCT International Publication Number WO 95/30766) (November 16, 1995).

This rejection is based on the language "such as" in claim 1, which permits the detection of any mutation in cytochrome P450 as the specific mutations following the phrase "such as" are mere options, not a specific requirement of the claimed invention.

Soderlund et al teach a method for determining a point mutation in a nucleic acid sample obtained from a cell (Abstract and Claims 1-5), comprising the steps of :

a) isolating and/or providing detectable amounts of single-stranded DNA from the sample by using known methods (Example 1, page 20, lines 30-34 and Examples 2-10, oligonucleotide and DNA sample Subsection);

b) hybridising the single-stranded DNA obtained in step a) with a detection primer comprising a plurality of nucleotide residues, the primer being complementary to a target nucleotide sequence immediately adjacent and 5' in relation to a defined point mutation of a single-stranded DNA of any gene (Examples 1-10, Polymerase chain reaction-amplification Subsection);

c) extending the primer using a polymerising agent in a mixture comprising one or more nucleoside triphosphates wherein the mixture includes at least one labelled nucleoside

triphosphate complememtary to either the first or second nucleic residue, and optionally one or more chain terminating nucleoside triphosphates (Examples 1-10, Polymerase chain reaction-amplification Subsection);

d) detecting the incorporation of the nucleoside triphosphates using the means, whereby it is determined whether the sample contains the point mutation of the particular gene being studied (Examples 1-10, Affinity-capture and identification of the variable nucleotides Subsection and claims 1-5).

Soderlund et al teach a method, wherein the single-stranded DNA isolated and/or provided in step a) is obtained by performing a modified amplification reaction in which one of the two amplification primers comprises a first attachment moiety bound to the primer, thereby obtaining a double-stranded amplification product in which only one of the strands comprises a first attachment moiety, where the first attachment moiety is one half of an affinity pair, and then simultaneously or sequentially in any order rendering the amplification product single-stranded and immobilizing the strand comprising the first attachment moiety to a solid support with the aid of the other component of the affinity pair, whereafter all unbound material is removed (Example 9, page 42, lines 9-27 and Example 10, page 44, lines 14-23 and Claim 13).

Soderlund et al teach a method, wherein the point mutation to be detected only comprises one altered nucleotide (Claims 3-5, Example 8, Page 38, line 20 to page 39, line 7 and Example 10, Page 44, line 28 to page 45, line 18).

Soderlund et al do not teach a method, wherein the mutation in cytochrome P450 isoform gene is detected to determine the ability of cells to metabolize a certain drug.

Goldstein et al. teach a method, wherein the mutation in cytochrome P450 isoform gene is detected to determine the ability of cells to metabolize a certain drug (Page 1, line 25 to page 4, line 25).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute and combine the method, wherein the mutation in cytochrome P450 isoform gene is detected to determine the ability of cells to metabolize a certain drug of Goldstein et al. with the method of determining specific nucleotide variations of Soderlundet al. since Goldstein et al state, "Genetic polymorphisms of P450 enzymes result in phenotypically-distinct subpopulations that differ in their ability to perform particular drug biotransformation reactions (Page 1, line 40 to page 2, line 2)". Moreover, Goldstein et al state, "Accordingly, it is important for both drug development and clinical use to screen drugs to determine which P450 enzymes are required for activation and/or detoxification of the drug. It is also important to identify individuals who are deficient in a particular P450 enzyme (Page 2, lines 10-15)". An ordinary practitioner would have been motivated to substitute and combine the method, wherein the mutation in cytochrome P450 isoform gene is detected to determine the ability of cells to metabolize a certain drug of Goldstein et al. with the method of determining specific nucleotide variations of Soderlundet al. in order to achieve the express advantages of a genetic polymorphism, as noted by Goldstein et al, which result in phenotypically-distinct

subpopulations that differ in their ability to perform particular drug biotransformation reactions and which provides method for both drug development and clinical use to screen drugs to determine which P450 enzymes are required for activation and/or detoxification of the drug and which is also important to identify individuals who are deficient in a particular P450 enzyme.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti , Ph.D., whose telephone number is (703) 306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237.

Arun Chakrabarti,

Patent Examiner,

June 11, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600